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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GABEL, GAILENE	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 03/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/492,214	STEMMLER ET AL.	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-7,9-16,19,21,23,33-36 and 42-47* is/are pending in the application.

4a) Of the above claim(s) *46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-7,9-16,19,21,23,33-36,42-45 and 47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) *2-7,9-16,19,21,23,33-36 and 42-47* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Restriction Election

1. Applicant's election of claims 2-7, 9-16, 19, 21, 23, 33-36, 42-45, and 47, filed 12/17/03 is acknowledged and has been entered. Claim 46 is withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being claim drawn to a non-elected invention. Accordingly, claims 2-7, 9-16, 19, 21, 23, 33-36, and 42-47 are pending. Claims 2-7, 9-16, 19, 21, 23, 33-36, 42-45, and 47 are under examination.

Applicant traverses the restriction requirement for reason that Examiner has not met the burden of establishing two or more independent and distinct claims. Applicant contends that in the instant application, Group I may include metal as the quenching substance while Group II includes a metal quenching substance.

Applicant's argument is not found persuasive because restriction requirements are set forth for reasons of patentable distinction between each independent invention so as to warrant separate classification and search. Specifically, each independent invention is presented with distinct structural and functional requirements, i.e. required use of metal as quenching substance and no requirement of metal as quenching substance. Therefore, literature search and examination of each of the methods are distinct. While searches for these two inventions would be expected to overlap, there is no reason to expect the searches to be coextensive.

The requirement is still deemed proper and is therefore made FINAL.

Rejections Withdrawn

2. The rejections of claims 1, 8, 17, 18, 20, 22, and 37-41 are now moot in light of Applicant's cancellation of the claims.

3. In light of Applicant's amendment, the rejection of claims 2-4, 6, 7, 9-14, 23, 34-35, 42, and 45 under 35 U.S.C. 102(e) as being anticipated by Hargreaves (US 6,121,055), is hereby, withdrawn.

4. In light of Applicant's amendment, the rejection of claims 9-13 and 34-35 under 35 U.S.C. 102(e) as being anticipated by Te Koppele et al. (US 6,127,139), is hereby, withdrawn.

5. In light of Applicant's amendment, the rejection of claims 2, 4, 6, 9-13, and 34-35 under 35 U.S.C. 102(b) as being anticipated by Saunders et al. (US 5,674,699), is hereby, withdrawn.

6. In light of Applicant's amendment, the rejection of claims 2, 4, and 9 under 35 U.S.C. 102(b) as being anticipated by Komives et al. (US 5,510,247), is hereby, withdrawn.

7. In light of Applicant's amendment, the rejection of claims 5, 15-16, 19, 21-22, 33, and 36-41 under 35 U.S.C. 103(a) as being unpatentable over Hargreaves (US 6,121,055) in view of Dixon et al. (US 5,381,224), is hereby, withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 2-7, 9-16, 19, 21, 23, 33-36, 42-45, and 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 42, step a) is vague and indefinite in reciting "capable of" because it fails to recite a positive limitation in the claim.

Claim 42, step a) is confusing in reciting, "suppressing signal from unbound labeled reagent" because it is unclear as to whether 1) the quenching substance suppresses signal as a result of binding between the labeled reagent and the analyte; thus, quenching effected upon bound labeled reagent; or 2) binding between the labeled reagent and the analyte causes the quenching substance to quench or suppress signal originating from unbound labeled reagent. Please clarify.

Claim 42, step c) is ambiguous in reciting, "the determination occurs" because it is unclear how a step of determination *occurs.* Perhaps, Applicant intends "determination is performed or effected". See also claim 5.

Claim 47, step a) is vague and indefinite in reciting "capable of" because it fails to recite a positive limitation in the claim.

Claim 47, step a) is confusing in reciting, "suppressing signal from unbound labeled analyte" because it is unclear as to whether 1) the quenching substance suppresses signal as a result of binding between the reagent and the labeled analyte; thus, quenching effected upon bound labeled analyte; or 2) binding between the reagent and the labeled analyte causes the quenching substance to quench or suppress signal originating from unbound labeled analyte. Please clarify.

Claim 47, step c) is ambiguous in reciting, "the determination occurs" because it is unclear how a step of determination *occurs.* Perhaps, Applicant intends "determination is performed or effected".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 2-4, 6, 7, 9-13, 35, 42-45, 47 are rejected under 35 U.S.C. 102(e) as being anticipated by Mirkin et al. (US Patent 6,361,944).

Mirkin et al. disclose a method of quantitative or qualitative determination of analyte by contacting a sample containing nucleic acid, i.e. analyte, with fluorescent labeled reagent such as nuclei acid (oligonucleotide) attached to a quenching substance that is coated or immobilized on a solid phase (substrate) (see columns 21-23 and 29-33). Oligonucleotides are useful in detecting target nucleic acids, i.e. bacterial antigens, viral antigens, cytokines (cancer), enzymes (see column 18, lines 18-65). Mirkin et al. further disclose exciting the sample so as to generate signal from the bound labeled nucleic acid, and then measuring the signal generated to thus obtain a qualitative or quantitative determination of the analyte. Fluorescent measurement

signals are generated by irradiation excitement of the fluorescent label using illumination by UV lamp (see column 31, lines 33-38). Preferred solid phase includes wells of microtiter plates (see column 21, lines 23-63). The quenching substance consists of metallic or semiconductor nanoparticles (see column 6, line 57 to column 7, line 4). The metallic quenching substance is preferably gold or silver and can be used with any assay format, i.e. affinity, sandwich assays (see column 16, line 29 to column 17, line 7 and columns 2-7). According to Mirkin et al., metal and semiconductor nanoparticles are known fluorescence quenchers with the magnitude of the quenching effect depending on the distance between the nanoparticles and the fluorescent molecule. In practice, binding (hybridization) of target nucleic acid to oligonucleotides causes the fluorescent labeled molecule to be spaced away from the nanoparticles; thus diminishing quenching of the fluorescence.

10. Claims 2-4, 9-11, 35, 42, 44, 45, 47 are rejected under 35 U.S.C. 102(e) as being anticipated by Selvin (US Patent 6,667,179).

Selvin discloses a method of qualitative determination (binding or unbinding) of analyte (ligand binding pair or second molecule) by contacting a sample containing the ligand, with a labeled reagent (receptor or first molecule) which comprises a fluorescent label (luminophore / fluorophore) that is immobilized on a solid phase (substrate) (see column 2, lines 38-67). The solid phase comprises a semiconductor which acts as a quenching substance (luminescence quencher). The labeled reagent for exemplary bindings includes antigen, antibody, nucleic acid, ligands and receptors for affinity and

immunoaffinity assays (see column 3, lines 44-55). The quenching substance consists of silicon (see column 4, lines 12-28). By quenching is meant that the semiconductor causes a decrease in the intensity and/or excited state of the luminescence. Selvin further discloses exciting the sample so as to generate signal, and then measuring the signal generated to thus obtain a qualitative determination of the analyte. Luminescence measurements signals are performed using luminometers (see column 5, lines 3-14).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 5, 14-16, 21, 23, 33, 34, and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al. (US Patent 6,361,944) in view of Hargreaves (US 6,121,055).

Mirkin et al. has been discussed supra. Mirkin et al. differ from the instant invention in failing to disclose that the well is cylindrical in shape. Mirkin et al. further differ from the instant invention in failing to disclose using a laser to provide a light beam.

Hargreaves discloses a method for detecting presence or amount of analyte in a system. Specifically, Hargreaves discloses a two-phase system wherein a first aqueous phase comprises an assay mixture containing the analyte, reactants (binding components, i.e. antibodies), label, and a primary layer which extends generally traversely across within a second solid phase which comprises a well on a microtiter plate (see column 13, lines 23-27 and column 9, lines 6-28). Hargreaves discloses that the wells may have numerous geometric configurations using different sizes, i.e. nanotiter, and shapes, i.e. cylindrical (see column 27, lines 1-16). In heterogeneous assays, the primary layer is selectively semi-solid or gel and separates bound from unbound label and binding reactants (see column 13, lines 38-41 and column 11, lines 43-52). A secondary layer across within the well may also contain assay reactants (see column 13, lines 47-50). The assay mixture is largely aqueous solution including components such as water, buffer, preservatives, and proteins (see column 5, lines 57-61). Hargreaves uses labeling substances including fluorophores, laser type dyes and luminescers (see column 24, line 58 to column 25, line 7 and column 22, lines 37-39).

Hargreaves teaches exciting fluorescent-labeled complexed binding pairs from the bottom region using beam from a laser diode and taking measurement signals therefrom using a detector, such embodiment prevents excitation of unbound or free labels in the system (see column 29, lines 26-29). A quenching substance such as a resonance energy transfer receptor like rhodamine where fluorescein is the label can also be incorporated into the binding assay system (see column 29, lines 30-43). Hargreaves finds application in specific binding assays such as competitive and sandwich heterogeneous assays as well as affinity or immunoaffinity assays for specific binding pairs including antigens and antibodies as well as nucleic acid complementary sequences (see columns 25-26 and column 8, lines 51-58).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate wells which are cylindrical in shape as taught by Hargreaves for use in the method of Mirkin because Mirkin is generic in the shape of microtiter well plate that can be used, and cylindrical shape as taught by Hargreaves constitutes an obvious variation of geometrical well configurations known in the art. Further, it would have been obvious to of ordinary skill in the art at the time of the instant invention to excite the sample of Mirkin using laser light beam as taught by Hargreaves because Mirkin is generic in the type of light beam used and laser is an obvious variation of irradiation or excitation beam source known in the art.

Mirkin et al. and Hargreaves differ in from the instant invention in failing to disclose 1) the volume, less than 1 ul and in the range of 50 to 100 nl, at which detection occurs in claims 5 and 23, respectively; 2) providing the well in the microtiter

plates as having a truncated pyramid or cone shape in claim 1; 3) providing the well having an aperture surface smaller than the floor surface in claim 15; and 4) the diameter, less than 40 um and less than about 20 um, of the exciting light beam directed to the sample volume as recited in claims 21 and 36, respectively; and the providing the sample carrier as a nanotiter plate as recited in claim 34.

However, these parameters, shape, and size requirements incorporated into affinity assays and systems constitute obvious modifications of parameters which are routinely varied in the art (e.g. volume, size, shape, etc.) and which have not been described as being critical to the practice of the invention. Therefore, it is maintained that the sample volume in the time of detection, i.e. 1 ul or 50-100 nl and the exciting light beam diameter in the sample volume, i.e. less than 40 um or about 20 um, are all result effective variables which the prior art references have shown may be altered in order to achieve optimum results. It has long been settled to be no more than routine experimentation for one of ordinary skill in the art to discover an optimum value of a result effective variable. "Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum of workable ranges by routine experimentation." Application of Aller, 220 F.2(454, 456, 105 USPQ 233, 235-236 (C.C.P.A. 1955). "No invention is involved in discovering optimum ranges of a process by routine experimentation." Id. at 458, 105 USPQ at 236-237. The "discovery of an optimum value of a result effective variable in known process is ordinarily within the skill of the ad." Application of Boesch, 617 F.2d 272, 276, 205 USPQ 215, 218-219 (C.C.P.A. 1980). Since Applicant has not disclosed that the specific limitations recited

in instant claims 5, 15, 16, 21, 33, and 36 are for any particular purpose or solve any stated problem and the prior art teaches that quantitative determinations in binding assays often vary according to the sample being analyzed and various parameters and variables appear to work equally as well, absent unexpected results, it would have been obvious for one of ordinary skill to discover the optimum workable ranges and parameters of the methods disclosed by the prior art by normal optimization procedures known in the binding assays.

12. Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al. (US Patent 6,361,944) in view of Hargreaves (US 6,121,055), and in further view of Dixon et al. (US 5,381,224).

Mirkin et al. and Hargreaves have been discussed supra. Mirkin et al. and Hargreaves differ from the instant invention in failing to teach that the measurement signal is obtained by spatially staggered measurement.

Dixon et al. disclose a scanning laser beam imaging or mapping system for macroscopic biological specimens which is capable of confocal and non-confocal imaging to be performed in fluorescence, photoluminescence, reflected light and other contrast mechanisms such as transmitted and scattered light (see Abstract and column 1, lines 5-19). Specifically, Dixon et al. teach obtaining spatially staggered measurements (spatially and spectrally resolved luminescence measurements) by measuring luminescence spectrum at each pixel position, then later mapping the changes in several spectral characteristics as a function of position in the specimen

(see column 5, lines 10-64). Dixon et al. find application of the system in gene sequencing or DNA mapping of fluorescent gels and other biological specimens that fluoresce upon excitation by laser radiation (see column 3, lines 29-33).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to obtain spatially staggered measurements as taught by Dixon of the signal generated from bound labeled reagent or bound labeled target nucleic acids analyte in the method of Mirkin as modified by Hargreaves because Mirkin and Hargreaves are generic with respect to the type of detection measurement used, and Dixon specifically taught application of spatially and spectrally staggered luminescence measurements combined with measurement of biological assay mixtures that produce any one of fluorescence, luminescence, scattered light, reflected light, carrier lifetimes, and others, upon irradiation.

13. For reason aforementioned, no claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (571) 272-0820. The examiner can normally be reached on Monday, Tuesday, and Thursday, 5:30 AM to 2:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gailene R. Gabel
Patent Examiner
Art Unit 1641
March 8, 2004

Christopher L. Chin

CHRISTOPHER L. CHIN
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